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(12) UK Patent Application (19) GB (11) 2 202 743 (13) A

(43) Application published 5 Oct 1988

(21) Application No 8807788

(22) Date of filing 31 Mar 1988

(30) Priority data
(31) 8704560 (32) 1 Apr 1987 (33) FR

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(51) INT CL*
A61K 9/08 31/17 31/41

(52) Domestic classification (Edition J):
A5B 170 410 411 41Y 480 48Y 542 54Y 565 56Y 586 58Y 644 64Y 664 66Y JB
U1S 2410 A5B

(56) Documents cited
GB A 2116425

(58) Field of search
A5B
Selected US specifications from IPC sub-class A61K

(54) Antifungals

(57) Compositions for topical application comprise at least 1% by weight, relative to the total weight of the composition, of miconazole nitrate or econazole nitrate dissolved in a mixture of water, urea and a water-soluble dissolving intermediary, the weight of urea not exceeding the weight of water present.

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ANTIFUNGAL COMPOSITION

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The present invention relates to an antifungal composition comprising miconazole nitrate or econazole nitrate which may be used in the treatment of fungal infections of the nails and/or the surrounding tissues.

Both miconazole nitrate and econazole nitrate are imidazole derivatives having good antifungal and antibacterial activity. They are especially recommended in the local treatment of candidiasis, dermatophytosis, pityriasis versicolor and onychomycosis.

The galenical forms hitherto proposed based on miconazole nitrate or econazole nitrate do not provide good bioavailability of the active principle since it is in suspension in the crystalline state. In order to provide improved bioavailability, solutions of the imidozale derivatives in fatty excipients, in particular in undecylenic acid, which improves their solubility, have been proposed in EP-A-0,064,830. However, such solutions are still not satisfactory as they are anhydrous, and consequently do not hydrate the nail. This reduces the bioavailability of the active principle.

Since both miconazole nitrate and econazole nitrate are insoluble in water and only very slightly soluble in an aqueous-alcoholic mixture, it has not hitherto been possible to obtain antifungal compositions containing these active substances in aqueous solution at concentrations that are

adequate to provide a good therapeutic effect.

The presence of water confers a particular advantage since it hydrates the nail so that the active principle can be delivered at a deep level.

We have surprisingly found that it is possible to obtain antifungal compositions containing miconazole nitrate or econazole nitrate in aqueous solution, by using urea as a solubilizing agent. The urea in an aqueous solution significantly increases the solubility of the miconazole nitrate and the econazole nitrate.

The present invention therefore provides an antifungal composition suitable for topical application comprising at least 1% by weight, relative to the total weight of the composition, of miconazole nitrate or econazole nitrate dissolved in a mixture of water, urea and a water-soluble dissolving intermediary, the weight of urea present not exceeding the weight of water present.

The composition may, for example, be in the form of a lotion, gel (a thickened composition) or varnish.

The urea increases the solubility of the miconazole nitrate or the econazole nitrate irrespective of the nature of the water-soluble dissolving intermediary used for the formation of the aqueous phase.

The miconazole nitrate or the econazole nitrate is preferably present, in the dissolved state, in an amount of from 1 to 2% by weight relative to the total weight of the composition.

The water is generally present in an amount of from 5 to 20% by weight, and the urea is generally present in an amount of from 1 to 20%, relative to the total weight of the composition.

The dissolving intermediary can be, for example, a primary or secondary alcohol, a ketone, a glycol or a glycol ether, or a mixture thereof.

The dissolving intermediary should not only be water-soluble, but also, in the case of varnishes, be capable of solubilizing a film-forming resin to leave a film after evaporation and/or penetration.

Examples of primary or secondary alcohols are methanol, ethanol, isopropanol, n-propanol and benzyl alcohol. Suitable ketones are acetone, diethyl ketone, diisobutyl ketone, ethyl butyl ketone, methyl isobutyl ketone and methyl propyl ketone. Examples of glycols and glycol ethers are ethylene glycol, propylene glycol, diethylene glycol, dipropylene glycol, ethylene glycol methyl ether, ethylene glycol ethyl ether and diethylene glycol methyl ether.

According to a preferred embodiment of the invention, the dissolving intermediary is ethanol or a mixutre of ethanol and propylene glycol.

When the composition is in the form of a gel, it contains a thickening or gelling agent such as a montmorillonite derivative, bentonite derivative, bentone, hectorite, kaolin, attapulgite, hydroxypropyl-guar, a

cellulose derivative such as methyl cellulose, hydroxymethylcellulose, hydroxybutylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylhydroxyethylcellulose or methylhydroxypropylcellulose, or a crosslinked polyacrylic acid such as that sold by Goodrich under the name CARBOPOL (Trade Mark).

The thickening or gelling agent is preferably present in an amount of from 0.5 to 2%, more preferably from 0.7 to 1.5%, by weight relative to the total weight of the composition.

When the composition is in the form of a varnish, it contains a resin which leaves a film remaining after evaporation of the solvent. Any polymer or copolymer compatible with the solvent may be used, for example, the polyvinylpyrrolidone/vinyl acetate polymer sold by Gaf Corporation under the name "PVP-VA E335", the polyvinyl acetate sold by Rhone-Poulenc under the name Rhodopas M60A (Trade Mark), the polyacrylamide sold by American Cyanamid under the name Gelamide 250 (Trade Mark), the hydroxymethylcellulose phthalate sold by Seppic under the name "HP55", the dimethylaminomethyl methacrylate/lower alkyl methacrylate sold by Rohm and Haas under the name Eudragit E100 (Trade Mark), the vinyl acetate/crotonic acid copolymer sold by National Starch under the name "Resin 28-1310", the methyl vinyl ether/butyl monomaleate copolymer sold by Gaf Corporation under the name "Gantrez ES 425" (Trade Mark) and a polymer based on alkyl acrylate or

methacrylate and acrylic or methacrylic acid.

The resin is generally present in an amount of from 7.5 to 30%, preferably from 10 to 20%, relative to the total weight of the composition.

The composition can, in addition, comprise other ingredients such as preservatives, antioxidants and, in the case of varnishes, plasticizers such as glycerol.

The present invention also provides an antifungal composition as defined above for use in a method of treatment of the human or animal body by therapy, in particular for use in the treatment of fungal infections of the nails or of the surrounding tissue.

The invention is now further described in the following Examples showing suitable antifungal compositions of the invention.

Example I Varnish:

Miconazole nitrate	2 %
Water	9.5 %
Urea	9 %
Absolute ethanol	25.5 %
Acetone	14 %
Polymer PVP-VA E 335 sold by the company GAF (50% strength solution	40 %

Example II Gel:

Econazole nitrate	1	%
Water	10	%
Urea	1	%
Propylene glycol	43.5	%
Absolute ethanol	43.5	%
Hydroxypropylcellulose sold by the company HERCULES under the name "KLUCEL H"	1	%

Example III Lotion:

Miconazole nitrate	1	%
Water	5	%
Urea	5	%
Propylene glycol	45.5	%
Absolute ethanol	43.5	%

Example IV Varnish:

Miconazole nitrate	2	%
Water	10	%
Urea	10	%
Absolute ethanol	64	%
Glycerol	2	%
Dimethylaminoethyl methacrylate/lower alkyl methacrylate polymer sold by the company ROHM and HAAS under the name "Eudragit E 100"	12	%

CLAIMS

1. An antifungal composition suitable for topical application comprising at least 1% by weight, relative to the total weight of the composition, of miconazole nitrate or econazole nitrate dissolved in a mixture of water, urea and a water-soluble dissolving intermediary, the weight of urea present not exceeding the weight of water present.

2. A composition according to claim 1 which comprises from 1 to 2% by weight, relative to the total weight of the composition, of the miconazole nitrate or the econazole nitrate dissolved in the mixture of water, urea and a water-soluble dissolving intermediary.

3. A composition according to claim 1 or 2 wherein the water is present in an amount of from 5 to 20% by weight relative to the total weight of the composition.

4. A composition according to any one of claims 1 to 3 wherein the urea is present in an amount of from 1 to 20% by weight relative to the total weight of the composition.

5. A composition according to any one of claims 1 to 4 wherein the dissolving intermediary is a primary or secondary alcohol, a ketone, a glycol or a glycol ether.

6. A compostion according to claim 5 wherein the primary or secondary alcohol is methanol, ethanol, isopropanol, n-propanol or benzyl alcohol.

7. A composition according to claim 5 wherein the ketone is acetone, diethyl ketone, diisobutyl ketone, ethyl butyl ketone, methyl isobutyl ketone or methyl propyl ketone.

8. A composition according to claim 5 wherein the glycol or glycol ether is ethylene glycol, propylene glycol, diethylene glycol, dipropylene glycol, ethylene glycol methyl ether, ethylene glycol ethyl ether or diethylene glycol methyl ether.

9. A composition according to claim 6 wherein the dissolving intermediary is ethanol or a mixture of ethanol and propylene glycol.

10. A composition according to any one of claims 1 to 9 which is in the form of a lotion, gel or varnish.

11. A composition according to claim 10 which also comprises a thickening or gelling agent in an amount of from 0.5 to 2% by weight relative to the total weight of the composition.

12. A composition according to claim 10 which also comprises a resin in amount of from 7.5 to 30% by weight relative to the total weight of the composition.

13. An antifungal composition substantially as described in any one of Examples I to IV.

14. An antifungal composition as defined in any one of claim 1 to 13 for use in a method of treatment of the human or animal body by therapy.

15. An antifungal composition as defined in any one of claims 1 to 13 for use in the treatment of fungal infections of the nails or of the surrounding tissue.